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Vitamin D in Relation to Myocardial Structure and Function after Eight Years of Follow-Up: The Hoorn Study

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Key Words
Vitamin D · Myocardial function · Myocardial structure · Epidemiology · Elderly

Abstract
Background and Aims: To investigate associations between baseline serum 25-hydroxyvitamin D [25(OH)D] levels and myocardial structure and function after 8 years of follow-up in older Dutch subjects. ***Methods:*** We included 256 subjects of the Hoorn Study, a population-based cohort. They underwent a standardized 2-dimensional echocardiogram at baseline between 2000 and 2001, and again between 2007 and 2009. We studied the association of 25(OH)D quartiles with echocardiographic measures of the left ventricular mass index (LVMI), left ventricular systolic function and markers of diastolic function using linear regression analyses. ***Results:*** At baseline, subjects had a mean age of 67.4 ± 5.2 years and 41.4% had prior cardiovascular disease (CVD). Low serum 25(OH)D levels were only associated with higher LVMI at 8-year follow-up in subjects without prior CVD and in subjects with low kidney function (median estimated glomerular filtration rate ≤77.5 ml/min/1.73m^2). The associations attenuated after adjustments for parathyroid hormone (PTH), which was associated with higher LVMI (g/m$^{2.7}$) in subjects with low kidney function (regression coefficient highest quartile 6.3, 95% CI: 0.2, 12.5). ***Conclusion:*** This study showed no strong associations of 25(OH)D with myocardial structure and function. However, PTH – a possible modifiable mediator in the relation between 25(OH)D and myocardial structure – was positively associated with LVMI in subjects with low kidney function.

Introduction

Worldwide, vitamin D deficiency is highly prevalent among older people, and is mainly caused by lifestyle and environmental factors that limit sunlight exposure to the skin [1]. Accumulating evidence suggests a role of low serum 25-hydroxyvitamin D [25(OH)D], which is the storage form of vitamin D, in the pathogenesis of various diseases such as autoimmune disorders, several types of cancers and cardiovascular diseases (CVD) [2, 3].

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A few prospective studies have found an inverse association of 25(OH)D levels with CVD risk in subjects without prior CVD. In the Health Professionals Follow-Up Study, men deficient in 25(OH)D (<15 ng/ml) had a 2-fold higher risk of developing myocardial infarction in 10 years compared to men with higher 25(OH)D levels (≥30 ng/ml) [2]. In the Framingham Offspring Study, subjects with severe 25(OH)D deficiency (<10 ng/ml) had a nearly 2-fold higher risk of a first cardiovascular event after 5 years of follow-up than subjects with higher levels of 25(OH)D (>15 ng/ml) [3].

Furthermore, findings in kidney patients support the observation that 25(OH)D deficiency induces hypertrophic growth of cardiomyocytes. Myocardial hypertrophy can lead to increased left ventricular (LV) mass. Kidney patients who were treated with calcitriol, which is the active form of vitamin D, showed regression of myocardial hypertrophy [4, 5]. Thus, vitamin D deficiency may in part explain the increased risk of CVD for kidney patients [4, 5].

Taken together, evidence supports the finding that low 25(OH)D levels induce myocardial hypertrophy [4–7]. This may suggest that cardiomyocytes require calcitriol for maintenance of myocardial function and could potentially explain the changes in cardiac morphology related to low 25(OH)D levels. LV hypertrophy may precede to LV diastolic dysfunction [8] and thereby 25(OH)D might also be associated with diastolic function.

Recent epidemiological studies have highlighted parathyroid hormone (PTH) not only as a biomarker of vitamin D status but also as an independent cardiovascular risk factor [9, 10]. We therefore aimed to analyze PTH as an exposure variable.

The investigation of the association between 25(OH)D and PTH in relation to myocardial structure and function represents a relevant step in unraveling the role of mineral metabolism markers in the prevention of CVD. The aim of this prospective study was to investigate the associations of 25(OH)D and PTH with changes in echocardiographic measures of myocardial structure and function in older men and women in the Netherlands.

Methods

Study Sample

The Hoorn Study started in 1989, including 2,483 men and women aged 50–75 years from the Netherlands. Detailed descriptions of the study concept have been published previously [11]. The current study was done involving 655 subjects who had examinations between 2000 and 2001 (considered baseline) [12]. Between 2007 and 2009, 214 subjects were not willing to participate in the follow-up examinations which resulted in 441 (67%) subjects who remained for longitudinal examinations.

Subjects who already had LV systolic dysfunction (LV ejection fraction <50%) or LV diastolic dysfunction (left atrial volume index >40 ml/m^2) at baseline (n = 34) were excluded. Subjects without baseline vitamin D measurements (n = 65) or with no or unsatisfactory data on echocardiography at follow-up (n = 13) were also excluded. Subjects without complete baseline and follow-up (n = 73) echocardiographic data were excluded since it would not be possible to study the change in echocardiographic data. Our study sample, therefore, consisted of 256 subjects for longitudinal analyses. All subjects provided written informed consent, and the Ethics Committee of the VU University Medical Center Amsterdam approved the study.

Vitamin D Status

Vitamin D status was assessed by measuring serum 25(OH) D levels with a competitive binding protein assay (DiasSorin, Stillwater, Minn., USA) [13], a valid marker of vitamin D status [14]. The interassay coefficient of variation was 10–15%. Serum PTH was determined with an immunoradiometric assay (Incstar Corp., Stillwater, Minn., USA). Laboratory measurements were conducted at the VU University Medical Center, Amsterdam.

Echocardiographic Measures

An ultrasound scanner (HP SONOS 5500; 2–4 MHz transducer, Andover, Mass., USA) was used to obtain an echocardiogram according to a standardized protocol. Two-dimensional and M-mode recordings were performed in parasternal long- and short-axis views, and apical four- and two-chamber views [15]. A senior cardiologist inspected each echocardiogram to ensure the quality of the measurements. All recordings were digitally stored and analyzed off-line.

Several echocardiographic estimates were measured as previously described [15]. In short, five estimates of myocardial structure and function were used: left ventricular mass index (LVMI, g/m$^{2.7}$); a second estimate of LV mass (LVMI/LV) volume index (ml·g/m^2); LV ejection fraction (%); left atrium volume index (LAVI) (ml/m^2), and a second estimate of diastolic function (LAV·LVMI in ml·g/m$^{2.7}$).

Additional Measurements at Baseline

Fasting glucose, postload glucose after an oral glucose tolerance test, fasting high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides were measured as described elsewhere [12]. Waist circumference (cm) was measured at the level midway between the lowest rib and the iliac crest. Blood pressure (mm Hg) was measured at the right-upper arm after 5 min of rest in a sitting position using a random-zero sphygmomanometer (Hawksley-Gelma Ltd, UK) and the average of two consecutive measurements was used. Arterial hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg and/or use of antihypertensive medication. As an estimate of kidney function, estimated glomerular filtration rate (eGFR) was calculated according to the modification of diet in the renal diseases formula [16]. Subjects filled out questionnaires to obtain information on medication use, smoking status and education level [13].

Statistical Analysis

Baseline characteristics, baseline echocardiographic data and changes in echocardiographic data over time are presented according to sex- and season-specific 25(OH)D quartiles. These were used because of the described sex difference in 25(OH)D levels in our study [13] and because of the well-known seasonal variations of 25(OH)D levels which are mainly attributed to annual differences in sun exposure of the skin [17]. We assumed that subjects in a specific 25(OH)D quartile are likely to remain in that quartile throughout the year, despite significant variations in absolute 25(OH)D levels [17]. Season classification was based on the date of blood sampling: winter (December–February), spring (March–May), summer (June–August), and autumn (September–November). We used linear regression analyses to examine linear trends across 25(OH)D quartiles, using the categorical variable of 25(OH)D as a continuous variable (sex- and season-specific quartiles entered as 1–4). A χ^2 test was performed to test for trends in the categorical variables across the quartiles of 25(OH)D. Differences between follow-up and baseline myocardial structure and function measures were calculated to investigate changes over time within quartiles of 25(OH)D.

Multiple linear regression analyses were used to study associations between baseline 25(OH)D (quartiles) and estimates of myocardial structure and function after 8 years of follow-up: LVMI, LVMI/LV volume index, LV ejection fraction, LAVI, and LAV·LVMI. The highest 25(OH)D quartile was considered as the reference group. We adjusted for the baseline value by adding independent variables to the regression models (i.e. LVMI at follow-up adjusted for baseline LVMI). The potential confounders considered were: waist circumference, BMI, physical activity, outdoor activities, blood pressure, cholesterol, triglycerides, glucose levels, antihypertensive drugs, lipid-lowering medication, beta-blockers, eGFR and PTH.

The first model was only adjusted for age (years). The second model was additionally adjusted for baseline echocardiographic measurements and lifestyle and metabolic variables based on the literature [18] or when regression coefficients changed by more than 10%: smoking status (yes/no), educational level (low, middle or high), outdoor activities (h/day), waist circumference (cm), low-density lipoprotein cholesterol (mmol/l) and use of lipid-lowering drugs (yes/no). Finally, we adjusted for PTH (pmol/l) which could confound but could also mediate the relationship between 25(OH)D and myocardial structure and function (if the latter was the case, adjustment would be inappropriate). Additionally, we treated 25(OH)D as a continuous variable to increase statistical power, adjusted for season, sex, baseline LVMI, and lifestyle and metabolic variables as mentioned above.

We tested for effect modification by prior CVD, because CVD treatment and self-care strategies could have already changed myocardial function. We also tested for effect modification by glucose tolerance status, according to which the subjects had been recruited. Furthermore, we tested for hypertension because this is a known risk factor for LV hypertrophy and we also tested for eGFR because low kidney function may result in lower conversion of 25(OH)D to active vitamin D [16]. When significant interaction terms were found ($p < 0.10$), analyses were stratified accordingly. Statistical analyses were conducted using the statistical program PASW 17.0 (SPSS Inc., Chicago, Ill., USA). All reported p values were two-sided and values <0.05 were considered statistically significant.

Results

Baseline 25(OH)D levels and complete longitudinal echocardiographic data were available for 256 subjects. The mean 25(OH)D level was 57.6 ± 19.1 nmol/l and 90 subjects (35.2%) had 25(OH)D levels <50 nmol/l. Baseline characteristics according to sex- and season-specific 25(OH)D quartiles showed that subjects with lower 25(OH)D levels were significantly older, had a larger waist circumference, higher blood pressure (systolic and diastolic), higher PTH levels and higher eGFR (table 1). None of the baseline myocardial structure or function measures showed a significant trend across the 25(OH)D quartiles. Subjects in the second 25(OH)D quartile had the most favorable myocardial structure and function measures: LVMI, LVMI/LV volume index, LAVI and LAV·LVMI were the lowest, and ejection fraction was the highest. Changes in myocardial structure and function during 8 years of follow-up did not differ significantly between the 25(OH)D quartiles (table 2). Included subjects with a baseline and follow-up measurement were younger (67.4 vs. 69.7 years), had less hypertension (62 vs. 67%) and lower waist circumference (93.1 vs. 94.1 cm) than subjects who had no follow-up measurements.

Results of the linear regression analyses in which follow-up echocardiographic measures were adjusted for their baseline values confirmed these findings by showing no association between 25(OH)D quartiles and the estimates of myocardial structures and function. After adjustment for potential confounders (data not shown), there was also no difference between the 25(OH)D quartiles. We found no effect modification by prior CVD, glucose tolerance status, hypertension or eGFR in these associations, except for LVMI. We stratified the analyses for LVMI by prior CVD (yes/no) and median eGFR (low kidney function $\leq$77.5 ml/min/1.73m^2 and high kidney function $>$77.5 ml/min/1.73m^2) because significant effect modification ($p < 0.01$) by these factors occurred for the association between 25(OH)D and LVMI.

In subjects without prior CVD, the lowest 25(OH)D quartile had a significantly higher LVMI after 8 years than the highest quartile (table 3, model 1). These results were attenuated when adjusting for smoking status, educational level, outdoor activities, waist circumference, low-density lipoprotein cholesterol and lipid-lowering medication (model 2, p trend 0.133), and the lowest 25(OH)D quartile lost its significance after adjusting for PTH (model 3, p trend 0.307). Similar results were seen when 25(OH)D was treated as a continuous variable: re-

Table 1. Baseline characteristics according to season- and sex-specific 25(OH)D quartiles

	Serum 25(OH)D				p trend
	quartile 1[a]	quartile 2[a]	quartile 3[a]	quartile 4[a]	
Mean, nmol/l	34.8	50.4	63.1	81.0	
Range (min–max), nmol/l	15.0–60.8	34.2–67.3	49.6–79.8	64.0–113.1	
Demographics					
n	60	66	67	63	
Age, years	69.7 ± 5.6[b]	66.8 ± 5.0	66.9 ± 4.9	66.3 ± 4.4	<0.001
Females, %	51.7	51.5	50.7	50.8	0.999
Education level					
Low, %	39.0	35.4	43.9	46.0	0.437
Intermediate, %	39.0	47.7	47.0	36.5	
High, %	22.0	16.9	9.1	17.5	
Prior CVD, %	46.7	37.9	37.3	44.4	0.631
Type 2 diabetes, %	23.3	12.5	17.9	14.3	0.391
Arterial hypertension, %	75.0	63.6	55.2	55.6	0.079
Lifestyle					
Cigarette smokers, %	15.0	15.2	7.5	9.5	0.417
Physical activity, h/day	3.0 ± 1.9	3.8 ± 2.8	3.5 ± 2.7	3.4 ± 2.3	0.560
Outdoor activities, h/day	0.9 ± 0.8	1.2 ± 1.2	1.4 ± 1.7	1.4 ± 1.2	0.012
Adiposity					
BMI	27.2 ± 3.4	26.8 ± 3.6	27.2 ± 2.9	26.3 ± 3.3	0.276
Waist circumference, cm	95.2 ± 10.4	93.4 ± 11.0	93.7 ± 11.0	90.0 ± 11.2	0.014
Metabolic variables					
Systolic blood pressure, mm Hg	146.6 ± 20.6	140.4 ± 20.2	135.7 ± 18.0	135.9 ± 18.6	0.001
Diastolic blood pressure, mm Hg	86.3 ± 12.6	83.4 ± 11.6	80.3 ± 10.4	81.6 ± 9.6	0.007
Fasting glucose, mmol/l	6.0 ± 1.0	6.0 ± 1.2	5.9 ± 1.0	5.8 ± 1.1	0.284
Postload glucose, mmol/l	6.9 ± 2.4	6.8 ± 2.0	7.1 ± 2.6	6.5 ± 2.0	0.465
HbA1c, %	5.9 ± 0.7	5.9 ± 0.6	5.8 ± 0.5	5.8 ± 0.5	0.060
Triglycerides, mmol/l	1.3 ± 0.7	1.6 ± 0.9	1.4 ± 0.7	1.3 ± 0.6	0.537
LDL cholesterol, mmol/l	3.5 ± 0.9	3.8 ± 0.9	3.8 ± 1.0	3.6 ± 0.7	0.715
HDL cholesterol, mmol/l	1.4 ± 0.4	1.4 ± 0.3	1.5 ± 0.4	1.5 ± 0.5	0.093
Parathyroid hormone, pmol/l[c]	6.9 ± 2.4	6.5 ± 4.2	5.7 ± 1.7	5.1 ± 1.4	<0.001
eGFR, ml/min/1.73m^2	82.8 ± 16.2	80.2 ± 15.0	79.9 ± 18.1	76.0 ± 12.0	0.021
eGFR <60 ml/min/1.73m^2, %	5.0	6.1	10.4	9.5	0.606
Echocardiographic measures					
LVMI, g/m$^{2.7}$	44.0 ± 14.3	37.9 ± 11.7	39.8 ± 10.0	39.8 ± 10.3	0.121
LVMI/LV volume index, ml·g/m^2	1.8 ± 0.5	1.6 ± 0.4	1.8 ± 0.6	1.7 ± 0.4	0.730
Ejection fraction, %	62.7 ± 6.8	64.3 ± 8.0	62.0 ± 6.7	63.6 ± 7.4	0.949
LA volume index, ml/m^2	23.4 ± 8.0	22.3 ± 7.2	22.5 ± 5.6	23.1 ± 6.4	0.905
LA volume[a] LVMI, ml·g/m^2	2,038 ± 1,383	1,705 ± 1,435	1,744 ± 736.7	1,740 ± 857	0.205

HbA1c = Hemoglobin A1c; HDL = high-density lipoprotein; LA = left atrium; LDL = low-density lipoprotein.
[a] Vitamin D quartiles are season and sex specific and therefore values may overlap.
[b] Data are presented as percentages or mean ± standard deviation.
[c] PTH n = 252.

Table 2. Eight-year changes in myocardial structure and function measures according to season- and sex-specific 25(OH)D quartiles

	Serum 25(OH)D				
	1st quartile (n = 60)	2nd quartile (n = 66)	3rd quartile (n = 67)	4th quartile (n = 63)	p trend
Myocardial structure					
LVMI, g/m$^{2.7}$	1.5 ± 16.1	0.7 ± 9.1	1.9 ± 10.7	0.0 ± 10.0	0.611
LVMI/LV volume index, ml·g/m^2	0.2 ± 0.7	0.3 ± 0.7	0.2 ± 0.7	0.2 ± 0.7	0.656
Systolic function					
Ejection fraction, %	–10.3 ± 11.4	–10.6 ± 9.6	–7.0 ± 9.8	–10.8 ± 11.5	0.783
Diastolic function					
LA volume index, ml/m^2	1.7 ± 11.0	2.9 ± 9.5	3.2 ± 7.3	1.4 ± 9.9	0.878
LA volume·LVMI, ml·g/m$^{2.7}$	88.5 ± 1,158	240 ± 878	392 ± 927	91.0 ± 1,317	0.857

Data are presented as mean changes ± standard deviation. LA = Left atrium; LV = left ventricle; LVMI = left ventricle mass index.

Table 3. Association of baseline 25(OH)D quartiles with LVMI (g/m$^{2.7}$) after 8 years of follow-up, stratified by prior CVD at baseline

	Serum 25(OH)D				
LVMI	1st quartile	2nd quartile	3rd quartile	4th quartile	p trend
No prior CVD	n = 32	n = 41	n = 42	n = 35	
Model 1	8.6 (2.6, 14.7)	2.5 (–3.1, 8.1)	4.6 (–0.9, 10.0)	reference	0.019
Model 2	6.0 (0.4, 11.6)	0.8 (–4.2, 5.8)	3.9 (–0.9, 8.7)	reference	0.133
Model 3	4.8 (–0.9, 10.4)	–0.3 (–5.4, 4.7)	3.4 (–1.3, 8.2)	reference	0.307
Prior CVD	n = 28	n = 25	n = 25	n = 28	
Model 1	–1.0 (–6.8, 4.9)	–5.5 (–11.4, 0.5)	1.3 (–7.3, 4.6)	reference	0.433
Model 2	–3.7 (–9.2, 1.7)	–5.4 (–11.1, 0.4)	–2.7 (–8.3, 2.8)	reference	0.113
Model 3	–4.4 (–9.9, 1.1)	–6.0 (–11.7, 0.3)	–3.1 (–8.6, 2.5)	reference	0.068

A positive regression coefficient implies higher LVMI. Model 1: adjusted for age. Model 2: as model 1 and also adjusted for baseline LVMI, smoking status, educational level, outdoor activities, waist circumference, low-density lipoprotein cholesterol and use of lipid-lowering medication. Model 3: as model 2 and also adjusted for PTH.

gression coefficient for 25(OH)D and LVMI in subjects without prior CVD was –0.15 (95% CI: –0.25, –0.04) and was attenuated after adjusting for lifestyle and metabolic variables to –0.09 (95% CI: –0.20, 0.02). In subjects with prior CVD, there was no clear association.

In subjects with low kidney function (eGFR ≤77.5 (ml/min/1.73m^2), only the lowest baseline 25(OH)D quartile had a significantly higher LVMI after 8 years than the highest quartile (table 4). When adjusted for potential confounders and PTH, the association disappeared. In patients with high eGFR (>77.5 ml/min/1.73m^2), 25(OH)D levels were not associated with LVMI after 8 years.

We performed additional analyses with PTH as the determinant, making sex- and season-specific quartiles of PTH with the lowest quartile as the reference group. We checked for effect modification which was only present for PTH with kidney function and LVMI. Linear regression analyses showed that PTH was positively associated with LVMI in subjects with low eGFR, with a significant trend over the quartiles (table 5). When PTH was used as a continuous variable, the results were similar in subjects with low kidney function (regression coefficient: 1.1, 95% CI: 0.17, 2.1) and disappeared after adjusting for potential confounders. In subjects with high eGFR, PTH was not associated with LVMI.

Table 4. Association of baseline 25(OH)D quartiles with LVMI (g/m$^{2.7}$) after 8 years of follow-up, stratified by median glomerular filtration rate at baseline

	Serum 25(OH)D				
LVMI	1st quartile	2nd quartile	3rd quartile	4th quartile	p trend
eGFR ≤77.5	n = 23	n = 29	n = 37	n = 39	
Model 1	9.9 (3.3, 16.6)	–2.3 (–8.4, 3.7)	2.3 (–3.3, 7.9)	reference	0.056
Model 2	6.2 (–0.2, 12.7)	–1.9 (–7.4, 3.6)	1.2 (–3.9, 6.3)	reference	0.265
Model 3	4.7 (–2.1, 11.5)	–2.7 (–8.3, 2.9)	0.5 (–4.6, 5.7)	reference	0.559
eGFR >77.5	n = 37	n = 37	n = 30	n = 24	
Model 1	–0.5 (–6.3, 5.3)	–1.4 (–7.0, 4.2)	0.4 (–5.5, 6.3)	reference	0.706
Model 2	–1.7 (–7.1, 3.6)	–2.2 (–7.3, 3.0)	–0.3 (–5.6, 5.0)	reference	0.411
Model 3	–2.4 (–7.7, 2.9)	–3.1 (–8.2, 2.1)	–0.2 (–5.4, 5.0)	reference	0.243

A positive regression coefficient implies higher LVMI. Model 1: adjusted for age. Model 2: as model 1 and also adjusted for baseline LVMI, smoking status, educational level, outdoor activities, waist circumference, low-density lipoprotein cholesterol and use of lipid-lowering medication. Model 3: as model 2 and also adjusted for PTH.

Table 5. Association of baseline PTH quartiles with LVMI (g/m$^{2.7}$) after 8 years of follow-up, stratified by median glomerular filtration rate at baseline

	Serum PTH				
LVMI	1st quartile	2nd quartile	3rd quartile	4th quartile	p trend
eGFR ≤77.5	n = 29	n = 34	n = 31	n = 32	
Model 1	reference	2.3 (–3.9, 8.4)	5.0 (–1.3, 11.2)	11.7 (5.4, 17.9)	<0.001
Model 2	reference	–0.3 (–6.0, 5.4)	3.7 (–2.0, 9.5)	6.8 (0.7, 12.8)	0.008
Model 3	reference	–0.3 (–6.1, 5.5)	3.8 (–2.0, 9.5)	6.3 (0.2, 12.5)	0.013
eGFR >77.5	n = 29	n = 32	n = 35	n = 30	
Model 1	reference	1.7 (–3.7, 7.1)	4.7 (–0.6, 10.0)	2.8 (–3.7, 7.1)	0.183
Model 2	reference	1.6 (–3.3, 6.5)	2.8 (–1.9, 7.5)	2.7 (–2.3, 7.6)	0.237
Model 3	reference	1.7 (–3.3, 6.7)	3.0 (–1.9, 7.9)	2.8 (–2.3, 7.8)	0.235

A positive regression coefficient implies higher LVMI. Model 1: adjusted for age. Model 2: as model 1 and also adjusted for baseline LVMI, smoking status, educational level, outdoor activities, waist circumference, low-density lipoprotein cholesterol and use of lipid-lowering medication. Model 3: as model 2 and also adjusted for 25(OH)D.

Discussion

In our study population of older subjects, only the lowest 25(OH)D quartile was associated with LVMI in subjects without prior CVD and in subjects with low kidney function. These associations were not independent of PTH since adjusting for PTH attenuated the associations.

The association between 25(OH)D status and echocardiographic measures has not been studied extensively. The limited number of previous studies have been inconsistent in the relationship between 25(OH)D and echocardiographic measures: two did [19, 20] and three [21–23] did not find an association between 25(OH)D levels and echocardiographic measures. It should be noted that most subjects in these studies suffered from heart failure which makes it hard to compare their results to ours in a population-based study.

In our study we observed effect modification by prior CVD and by kidney function (eGFR) with regard to the associations of 25(OH)D levels and LVMI. This suggests

that it is more likely that 25(OH)D is involved in hypertrophic cell growth, which may result in higher LVMI in the long run, than in diastolic function [24]. In subjects without prior CVD and in subjects with low kidney function, only the lowest 25(OH)D quartile was associated with higher LVMI. This could be due to the fact that adverse effects of 25(OH)D may be confined to lower levels of 25(OH)D.

The findings in subjects with lower eGFR were not unexpected given that kidney-specific 1α-hydroxylase activity [which catalyzes 25(OH)D to calcitriol] parallels the decline in residual renal function [25]. Decreased synthesis of calcitriol already occurs at eGFR values <90 ml/min/1.73m^2 [16]. Stratification based on the median eGFR led to a stratum in which the subjects had an eGFR ≤77.5 ml/min/1.73m^2 which suggests decreased synthesis of calcitriol. It was remarkable that the lowest 25(OH)D quartile had a significantly higher eGFR than the other quartiles. An explanation could be that low 25(OH)D may only be harmful in the case of low kidney function, although we cannot demonstrate this based on our observational data.

Small trials in renal patients did show significant associations between vitamin D and LVMI [4, 5, 26]. Kidney patients who were treated with calcitriol showed regression of cardiac hypertrophy [4, 5]. The kidney is the main source for circulating calcitriol which could imply that reduced amounts of circulating calcitriol limit the function of cardiomyocytes and induce myocardial proliferation [1, 16]. In subjects with prior CVD, opposite trends were observed as lower 25(OH)D levels were associated with lower LVMI. CVD treatment and lifestyle changes in subjects with prior CVD may change myocardial function, which could be an explanation for the lower LVMI in this subgroup.

We noticed that the associations between 25(OH)D and LVMI in subjects without prior CVD and low kidney function were not independent of PTH. After adjusting for PTH the association of 25(OH)D and LVMI was attenuated. As PTH could be a mediator of 25(OH)D and LVMI, we investigated PTH as a determinant in the relation with echocardiographic measures.

PTH was significantly associated with higher LVMI in subjects with a lower kidney function. This suggests that PTH is more strongly associated with LVMI than 25(OH)D. Although PTH and 25(OH)D are strongly interrelated, PTH levels can also be substantially influenced by other factors, e.g. calcium and phosphate intakes [16]. The relationship between PTH and LVMI was only visible in subjects with lower eGFR. A rise in serum PTH is one of the first detectable mineral metabolism disturbances of chronic kidney disease [27]. In our study, after adjustment for the residual eGFR (continuously), the observed association for PTH in subjects with low eGFR was slightly more pronounced. A recent meta-analysis suggests that vitamin D supplementation decreases PTH in chronic kidney disease patients [28] and low 25(OH)D predicts mortality in these patients [29]. In addition, vitamin D supplementation decreased mortality significantly in elderly women [30]. It should be elucidated whether improvements in mineral metabolism markers are important for cardiac outcomes [31, 32].

The observed positive association between serum PTH levels and LVMI is consistent with the results of other studies [33, 34]. From clinical studies there are also indications that PTH may contribute to the development of LV hypertrophy. In patients with end-stage renal disease who have secondary hyperparathyroidism [35], and also in patients with primary hyperparathyroidism [36], there is a strong relation between LVMI and PTH. The underlying mechanism is not completely known; however, PTH may influence intracellular signaling by an increase of intracellular calcium in the cardiomyocytes. PTH receptors have been demonstrated in the heart, and in vitro PTH induces hypertrophy of cardiomyocytes [37]. In addition, PTH activates protein kinase C which could lead to hypertrophic growth and expression of fetal-type proteins in cardiomyocytes [37]. This hypertrophic effect of PTH might contribute to the increase in LVMI.

A strength of this study is the detailed recordings of myocardial structure and function measurements over an extended period in a well-defined population-based cohort of older persons. Other studies have investigated 25(OH)D and myocardial structure and function in a cross-sectional setting in heart failure patients [19–21, 23], or in small clinical trials in kidney patients [4, 5, 26]. Our study allowed us to prospectively investigate 25(OH)D and myocardial structure and function in older men and women which gives insight to the role of 25(OH)D in cardiac diseases. There are also potential limitations of this work. The present study is a selected sample of the initial population-based cohort of the Hoorn Study. Moreover, missing data on echocardiographic measures may not have been missed at random, but be related to conditions such as obesity or underlying cardiac abnormalities. Therefore, generalizations about the associations of 25(OH)D and PTH with LVMI in the older population as a whole are limited, and are probably underestimated because subjects with more cardiac abnormalities were lost to follow-up. In addition, subgroup

analyses allowed us to get more insight into the underlying mechanisms, although they may be underpowered. When treating 25(OH)D and PTH as continuous variables, the results were consistent; however, these analyses cannot take into account a threshold effect of low 25(OH)D. Also, the observational design cannot exclude the possibility of reverse causation. Furthermore, this study was not designed to investigate longitudinal changes in myocardial structure and function. It should also be noted that we only had a single measurement of 25(OH)D and PTH which may not adequately reflect long-term status. Future studies could benefit from repeated follow-up measurements and a larger sample size.

In conclusion, 25(OH)D levels were not strongly associated with myocardial structure and function. The associations were not independent of PTH since adjusting for PTH attenuated the associations. PTH was positively associated with LVMI in subjects with low kidney function and is a potentially modifiable mediator in the relation between 25(OH)D and myocardial structure in a general older population. Future studies that investigate determinants of CVD should consider PTH levels, especially in subjects with decreased kidney function.

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Disclosure Statement

None declared.

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